UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,437	03/20/2006	Walter Gumbrecht	32860-000900/US	6672

30596 7590 09/17/2008
HARNESS, DICKEY & PIERCE, P.L.C.
P.O.BOX 8910
RESTON, VA 20195

EXAMINER	
THOMAS, DAVID C	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
09/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,437	GUMBRECHT ET AL.	
	Examiner	Art Unit	
	DAVID C. THOMAS	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15 and 17-19* is/are pending in the application.

4a) Of the above claim(s) *11-15 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/13/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed June 16, 2008 is acknowledged. Claims 1, 3, and 4 (currently amended) and 5-10, 17 and 18 (previously presented) will be examined on the merits. Claim 11 (currently amended) and claims 12-15 and 19 were previously withdrawn. Claims 2 and 16 are newly canceled.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 3, 4, 7, 8 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (U.S. Patent Pub. No. 2002/0155586) in view of Frechet et al. (U.S. Patent Pub. No. 2004/0101442).

Cheng teaches a method for PCR amplification and detection of nucleotide sequences (for overview, see Abstract), comprising:

using a reaction layer for binding of probe molecules and an array of a plurality of microspots forming analytical positions (a flow cell comprises an electronically addressable microarray, paragraph 60, lines 1-6 and Figure 5; the system may include a permeation layer overlaying the electrodes, and the probes may be coupled to the permeation layer, paragraph 24, lines 1-3 and claims 5 and 6), said microspots including as probe molecule at least one immobilized oligonucleotide which is hybridizable with a target sequence to be identified of a DNA fragment (nucleic acid probes are attached to the microarray for the purpose of detection of nucleic acids of interest such as amplification products, paragraph 34, lines 1-8 and paragraph 91, lines 1-8);

applying an analyte solution including PCR reagents and a plurality of target sequences to the microspots in such a way that it completely covers the array (the flow cell provides a compartment for containing biological sample materials and buffers to be layered on top of the microchip, including those needed for PCR amplification, paragraph 55, lines 5-15 and paragraph 61, lines 4-6);

subjecting the array to a thermocycling process to amplify the target sequences (heating element, part 12 of Figure 5, can be used for temperature cycling for nucleic

acid PCR amplification within the flow cell, paragraph 56, lines 8-12 and paragraph 77, lines 7-11); and

detecting hybridization events on probe molecules immobilized at one analytical position with the aid of a microelectrode arrangement (target species such as amplified products are electronically addressed to specified capture pads or coated electrodes for capture by anchored capture oligonucleotides, paragraph 92, lines 1-5, for detection using fluorophore-labeled reporter probes and a CCD-based optical imaging system, lines 12-16).

With regard to claims 2-4 and 16, Cheng teaches a method wherein a reaction layer, such as a hyrdogel based on acrylamide and having coupling groups for covalent binding of probe molecules is used (microchips are coated with a permeation layer such as a hydrogel of acrylamide which can be coupled with probes, paragraph 24, lines 1-3, paragraph 60, lines 14-21 and paragraph 92, lines 1-10).

With regard to claims 7, 8 and 17 Cheng teaches a method wherein an analyte solution is used which includes an external primer pair (a concentrated amplification reagent is introduced into the flow cell and contains primer pairs flanking the spa Q and inv A gene target region such that any variations with the genes will be amplified, paragraph 79, lines 6-15 and paragraphs 80-83).

Cheng does not teach a method for PCR amplification and detection of nucleotide sequences using a hydrophilic reaction layer having coupling groups for covalent binding of probe molecules, including a cross-linkable hydrogel based on acrylamide with either maleic anhydride or glycidyl (meth)acrylate as coupling groups.

Frechet teaches methods of grafting of polymer surfaces for microfluidic devices such as a "lab on a chip" that includes attachment of polymer chains having functional groups such as hydrophilic or reactive groups comprising acrylamide that bears functional groups including glycidyl methacrylate (paragraph 6, lines 1-17, paragraph 27, lines 1-10, paragraph 28, lines 1-3 and paragraph 29, lines 1-7).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Cheng for making and using an integrated system such as a chip for amplification and detection of nucleic acid targets directly on the chip device with the methods of Frechet for making similar lab-on-a-chip devices that can contain any of a variety polymers grafted to the surface that have functional groups attached that would be useful for covalent attachment of the oligonucleotide capture probes taught by Cheng. Thus, an ordinary practitioner would have been motivated to combine the methods of Cheng and Frechet since the substrates containing capture probes taught by Cheng, which can be formed in the permeation layer (Cheng, paragraph 24, lines 1-3), are highly suitable for being formed above the thermoplastic polymer surfaces taught by Frechet used for making microfluidic devices. Frechet teaches the formation of first and second monomers which are used to form porous layers within a microfluidic channel by a photopolymerizing technique, followed by addition of a third layer comprising the polymer with functional groups (paragraph 27, lines 4-10, paragraph 31, lines 1-17 and paragraph 32, lines 1-3), since this layer can contain the capture probes immobilized in the permeation reaction layer needed for detection by hybridization of amplified

products to the capture probes. The permeation layer is useful for protecting the biomolecules of interest from the electrochemistry occurring at the electrode surface (Cheng, paragraph 60, lines 14-21) and would be further protected by the additional layer or layers taught by Frechet that are attached closest to the chip surface under the permeation layer.

5. Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (U.S. Patent Pub. No. 2002/0155586) in view of Frechet et al. (U.S. Patent Pub. No. 2004/0101442) as applied to claims 1, 3, 4, 7, 8 and 17 above, and further in view of Ghodsian, B. (U.S. Patent Pub. No. 2002/0115293).

Cheng and Frechet together teach the limitations of claims 1, 3, 4, 7, 8 and 17, as discussed above.

With regard to claim 5, Cheng also teaches a method wherein a biochip including a substrate layer and an insulating layer connected therewith is used, the side of the insulating layer, which faces away from the substrate layer, carrying the electrode arrangement and the reaction layer (an electronically addressable microarray is mounted onto a substrate, to the back of which is attached a ceramic heater, while a protective permeation layer coats the microchips, facing away from the substrate, and protects the biomaterials from being directly exposed to the electrodes in the microchips, paragraph 60, lines 1-21 and Figure 5).

However, neither Cheng nor Frechet teach a method using a biochip comprising a substrate comprising a semiconductor layer wherein the layer is a silicon layer.

Ghodsian teaches the making of and use of devices for DNA sequencing including lab-on-a-chip devices comprising a substrate that are semiconductors composed of silicon that are useful for integration of active circuits (paragraph 201, lines 1-11).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Cheng and Frechet for making and using an integrated system such as a chip for amplification and detection of nucleic acid targets directly on the chip device with the methods of Ghodsian for making and using similar lab-on-a-chip devices for DNA sequencing since both systems use devices comprising substrates with integrated electronic circuitry for performing or controlling biological reactions, including DNA synthetic processes such as PCR and DNA sequencing. Thus, an ordinary practitioner would have been motivated to combine the methods of Cheng, Frechet and Ghodsian since the substrates taught by Cheng and Frechet are highly suitable for being formed of the semiconductor silicon as taught by Ghodsian since this material is ideal for micromachining and the integration of electronic circuits (Ghodsian, paragraph 201, lines 1-7) needed for detection of hybridization of amplified products to capture probes immobilized in a reaction layer, which can be attached to the silicon substrate in the devices of Cheng and Frechet to form the bottom layer of the flow chamber (Cheng, paragraph 61, lines 1-6).

6. Claims 9, 10 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (U.S. Patent Pub. No. 2002/0155586) in view of Frechet et al. (U.S.

Patent Pub. No. 2004/0101442) as applied to claims 1, 3, 4, 7, 8 and 17 above, and further in view of Strizhkov et al. (BioTechniques (2000) 29:844-846, 848, 850-852, 854, 856-857).

Cheng and Frechet together teach the limitations of claims 1, 3, 4, 7, 8 and 17, as discussed above.

However, neither Cheng nor Frechet teaches a method wherein a target that is first amplified in solution using an external primer and wherein the products are further amplified using internal primers immobilized within a reaction layer.

Strizhkov teaches a method of PCR amplification on a microarray using solution-based forward and reverse primers as well as internal primers immobilized inside a gel pad (p. 848, column 1, line 46 to column 2, line 17).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Cheng and Frechet for making and using an integrated system such as a chip for amplification and detection of nucleic acid targets directly on the hyrdogel layer of the chip device with the methods of Strizhkov, who also teaches methods of PCR amplification on a microarray using primers both in solution and immobilized on a surface such as a gel pad. Thus, an ordinary practitioner would have been motivated to combine the methods of Cheng, Frechet and Strizhkov since the methods of PCR amplification taught by Strizhkov using both solution-phase outer primers and solid-phase inner primers can be readily adapted to the microarray methods of Cheng wherein amplification can first take place, as it normally does, in the chamber of the flow cell using solution-based outer primers,

followed by capture of the amplification products by immobilized capture probes that also serve as inner forward primers to initiate a second round of amplification on the surface of the hydrogel layer. This modified system is similar to nested primer amplification and is useful for increasing the specificity of the procedure (Strizhkov, p. 848, column 2, lines 12-16). Amplification products can then be detected with the microelectrode system of Cheng using either light-based detection or a direct electrochemical detection system (Cheng, paragraph 95, lines 7-11).

Response to Arguments

7. Applicant's arguments filed June 16, 2008 have been fully considered but they are not persuasive.

The Claim Objections have been withdrawn in light of amendments to the claims.

Applicant's additional arguments with respect to the previous rejections of record have been noted, but are moot in view of the rejection of the claims based on new grounds. These include the arguments regarding the amendment of claim 1 citing the use of a hydrophilic reaction layer having coupling groups for covalent binding of probe molecules. This limitation is taught by the newly cited reference of Frechet (U.S. Patent Pub. No. 2004/0101442) and these claims are now rejected by Cheng in view of Frechet under 35 U.S.C. 103(a).

With regard to the argument that Cheng fails to teach or suggest a method for PCR amplification and detection that includes "detecting hybridization events on probe molecules immobilized at one analytical position with the aid of a microelectrode", the

Examiner asserts that this limitation is written such that "with the aid of a microelectrode arrangement" could refer to either the detection itself or the immobilization step. Regardless of the interpretation, Cheng teaches a method wherein PCR amplified products are electronically addressed to specified capture pads or coated electodes for capture by hybridization to anchored capture oligonucleotides (paragraph 92, lines 1-5). These hybridization events are ultimately detected using a CCD-based optical imaging system (paragraph 92, lines 12-16), but the fact remains that the hybridization events are detected after hybridization with the aid of a microelectrode arrangement, as cited in the claims, since the detection comprises both hybridization and optical detection of the hybridization, and the electrode plays a central role in facilitating the hybridization of the products to the capture probes.

Conclusion

8. Claims 1, 3-10, 17 and 18 are rejected. No claims are allowable.

Correspondence

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David C Thomas/
Examiner, Art Unit 1637

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637